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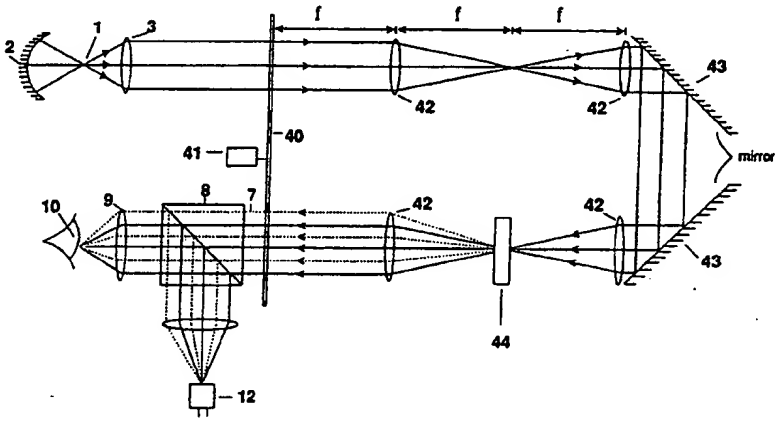


(57) Abstract

A method and apparatus for determining non-invasively the presence and/or concentration of blood analytes such as glucose in an animal, particularly a human animal. The apparatus comprises a light source (1) for producing a polychromatic light beam and means (4) for modulating the polychromatic light beam such that the modulation frequency is dependent upon the wavelength of light within the beam. The modulated light beam is caused to impinge upon a body part, preferably the front surface (10) of the eye of the animal so that blood analytes interact with the light beam and perturb the spectral distribution of light within the beam. Spectral information is extracted from the resulting light beam by detecting the beam at a plurality of modulation frequencies. The measurements may be linked to pulse measurements in a manner similar to pulse oximetry. The light beam may also be used to heat the body part to a desired temperature. A moulding (23) locates the light source and detector in a fixed location with respect to facial features of the animal. Various methods, including the use of polarisers and CCD detector arrays, are proposed to minimise the effect of specular reflection.

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"Method and Apparatus for
Non-Invasive Blood Analyte Determination"

This invention relates to the determination of blood analytes by a non-invasive method. Although the method itself is a general one, and can be used for a wide variety of materials present in blood, it is of particular interest in the non-invasive measurement of substances of interest in diabetes, such as glucose and glycated haemoglobin.

Blood glucose level testing is almost universally regarded as the first line in maintaining the control of diabetes. Typically, it may be desirable for the blood glucose level of a diabetic patient to be monitored several times during a day. The most common method of blood glucose level testing in current practice uses test strips to which a blood sample is applied. This requires a small blood sample to be withdrawn, usually by pricking the finger. The strips are usually tested using a portable battery operated glucose meter which reads the strips quantitatively. Obviously, it is undesirable for repeated blood samples to be taken from patients, and much interest has focused in recent years on non-invasive techniques for blood measurement.

Examples of techniques which have been investigated are:

- Near and mid infrared spectroscopy;
- photoacoustic spectroscopy;
- measurement of ocular focal properties;
- measurement of optical rotation in the aqueous humor of the eye;
- analysis of gingival crevicular fluid;
- Raman spectroscopy.

One of the most promising techniques so far is based on spectroscopy in the near infrared region (NIR).

EP-A-0160768 discloses a technique for measuring glucose by a non-invasive infrared technique in which a body part (typically a finger) is irradiated with one or more pairs of wavelengths in the region of from 1000 to 2700 nm, and detecting the transmitted or reflected radiation. A broad band optical source is filtered to produce desired wavelengths one after the other. The wavelengths are chosen such that the intensity of collected light at at least one wavelength $\lambda_g$ depends on the glucose concentration present, while the collected intensity at at least one other wavelength is in principle independent of the glucose concentration present. The intensity measurements are converted to measure the glucose concentration by standard techniques of NIR spectroscopy.

The wavelengths $\lambda_g$ are chosen from 1575, 1765, 2100, and 2270 $\pm$ 15 nm.

Because the absorption peaks attributable to glucose in the NIR overlap substantially with other materials present (including, for example, water), it is very difficult to obtain accurate measurements by the method disclosed, in particular for the range of glucose concentrations normally present in blood, i.e. in the range of from 2 to 10 mmol/litre.

WO/90/07905 also relates to the determination of blood glucose, using NIR. In this disclosure, a body part, again generally a finger, is irradiated using NIR of a number of different frequencies using an array of light emitting diodes (LEDs). Interference filters are employed to restrict the response of each detector and/or the emission of each LED to a particular NIR band, and calibration algorithms are used to relate glucose

levels to a linear combination of the detected bands. The use of a greater number of wavelengths improves sensitivity, and enables accuracy to be improved over the device of EP-A-0160768.

Most of the prior art NIR methods recommend the use of fingers, ear lobes, pinches of skin or the like, for the NIR measurement. All of these body parts have a number of disadvantages. In particular:-

1. All tend to experience substantial variations in temperature, for example of the order of 5°C or so, which can have a strong effect on the absorption strength and absorbtion wavelength of water present in the tissue.
2. They tend to be pigmented to an extent which varies widely from individual to individual.
3. They tend to have levels of body fat which can vary widely from individual to individual. This also can have a large effect on the measured glucose level.

We have now determined that the front surface of the eye is greatly superior to other body surfaces in the above, and also in a number of other important respects.

In accordance with a first aspect of the present invention, there is provided a method for determining non-invasively the presence and/or concentration of blood analytes in an animal which method comprises,

a. illuminating a surface of the body of the animal with infra red radiation, and

b. detecting infrared radiation reflected from the said surface and analysing the spectrum of the said reflected radiation to determine the concentration of the said analytes, wherein the said surface is the front surface of the eye.

As indicated above, the front surface of the eye has a number of advantages over other surfaces which have previously been proposed for non-invasive NIR spectroscopy for blood analyte (in particular glucose) determination.

In particular:-

1. the eye tends to have a very stable temperature, as compared with many other parts of the body,
2. it has levels of pigmentation which are relatively low, and are not subject to wide variation from individual to individual, and similarly has levels of fat which are not subject to such wide variation.

In addition, the eye has a number of other advantages for such measurement. Particularly, the front surface of the eye (the white of the eye), and the adjoining tissues (for example, in the corner of the eye) are particularly well supplied at their surface with blood vessels. The superficiality of the blood vessels in the eye enables reflection spectral measurements to be made from the eye at wavelengths which would be unsuitable for other body parts. This is because the blood vessels in other body parts are situated sufficiently far below the tissue surface that infrared radiation does not penetrate to them in significant amounts.

A further advantage of the surface ocular tissue is that it is relatively simple in structure and does not give rise to high levels of scattering. An additional advantage of carrying out measurement on the eye is that, because the surface is relatively smooth and is maintained in a moist condition, specular reflection occurs at relatively well defined angles, and it is therefore relatively easy to separate specular refection from diffuse reflection. It is the defuse reflection which carries the bulk of the spectral information representative of blood analyte levels.

In order to be able to determine reflected light from the front surface of the eye, means must be provided both for illuminating the said front surface, and for detecting light which is diffusely reflected (backscattered) from the illuminated surface. It is also necessary to provide means of locating either or both of the illuminating means and the detecting means, with respect to the facial features of the individual concerned.

Accordingly, in a further aspect of this invention, there is provided apparatus for determining non-invasively the presence and/or concentration of blood analytes in an animal comprising:-

a. means for illuminating a surface of the body of the animal with infrared radiation

b. means for detecting infrared radiation reflected from the said surface and for analysing the spectrum of the said reflected radiation to determine the presence and/or concentration of the said analytes, characterised in that the said surface is the front surface of the eye, and in that the apparatus includes means for locating the illumination means and/or the detecting means in a fixed location with respect to facial features of the animal.

The location means may preferably be a molding shaped to fit the particular face contours of the individual, for example the eye socket and/or nose of the individual. In a particularly preferred embodiment, a "standard" assembly carrying the illumination means and detecting means may be provided, and adapted to be fixed in a defined location to a molding shaped to the facial contours of the particular individual in question, so that, after the molding has been produced for that individual, the device may thereafter reproducibly be located in the same place. In a further embodiment, the device may be specially adapted so as to

focus on the edge regions of the eye which are particularly strongly supplied with blood vessels, and in particular the inner and outer corners of the eye.

In a further preferred embodiment of the invention, the device is provided with means for minimising the effects of specular reflection. In one embodiment, this may be done by so positioning the illumination means and the detector on the device so that specular reflection is substantially eliminated. For example, the device may be so orientated as to ensure that specularly reflected light does not reach the detector. In an alternative embodiment, the detector may be such as to be capable of detecting spatial variations in the reflected signal. For example, the detector may include a CCD array. The provision of such an array enables the location of the specular reflection to be readily ascertained, and, once ascertained, compensation may be applied to minimise its affects (for example by ignoring entirely the region in space in which the specular reflection occurs).

In a further alternative embodiment of this aspect of the invention, means are provided for discriminating between diffuse reflection and specular reflection from the eye surface based on the extent of polarization of the light on reflection. This may take the form of a polarizer associated with either the illumination means, the detecting means, or both, so orientated as to minimize the signal obtained from specular reflection. For example, a polariser may be inserted in the light beam to linearly polarise the light incident on the eye perpendicular to the plane of incidence. An analyser, also consisting of a polariser, may be inserted in the beam following its reflection from the eye. This polariser is orientated so as to block specularly reflected light from the eye. For example, the analyser may be crossed with respect to the

polariser. Circularly polarised light might also be used. A wave plate may also be used in conjunction with polarising elements.

A further aspect of the invention is concerned with the nature of the instrument itself, and of the NIR bands which are detected. The device disclosed in WO90/07905 indicates the desirability of measuring absorption at a number of points in the NIR spectrum, and combining the results obtained from these points in order to obtain quantitative results which indicate more accurately the presence of analytes present. This reference relies however on the use of individual LEDs and/or detectors. This results in a device which is mechanically very complex, and therefore difficult and expensive to produce.

Furthermore, WO90/07905 describes measurements made at wavelengths of up to about 1100nm, a region of the spectrum which is detectable using low-cost silicon detectors. However, glucose absorption in this region is very weak, and the absorptions overlap very strongly with water absorption. Operating at longer wavelengths in principle offers a way of decreasing the overlap between absorption bands. However, detectors for use at longer wavelengths are more expensive, and the use of individual detectors for each absorption band is therefore very expensive if longer wavelengths are to be detected.

It is known that it is possible to encode different NIR wavelengths by modulating them at a frequency which is dependent upon the wavelength of the radiation over a relatively broad band. For example, the so called "mock interferometer" described by Lawrence Mertz ("Transformations in Optics", Lawrence Mertz, John Wylie & Sons, Inc., New York, 1965) describes a device in which different wavelengths are encoded with different modulation

frequencies, using a rotating grating, onto which an image of the grating is formed. The device is said to be useful in the measurement of planetary spectra.

The device in question was viewed as something of a curiosity when it was proposed in the mid-60s, and so far as we are aware it has never been produced commercially.

We have determined however that modulating a light beam at a frequency dependent upon its wavelengths, and subsequently demodulating the signal obtained from the reflected light, in order to obtain a NIR spectrum, is a particularly advantageous method of determining the NIR spectrum of body parts, for blood analyte determination. The use of such a system has the substantial advantage that it is not necessary to provide separate LEDs and filters for each frequency which it is desired to investigate, but nevertheless a very large number of frequencies, for example twenty frequencies or more, may be separately investigated, using apparatus which is mechanically very simple. Discrimination between the signals obtained at the various frequencies may be carried out using suitable electronic frequency filters, for example discrete RC circuits tuned to the frequencies of interest, or a lock-in amplifier and frequency synthesizer. The filter analyses the intensity of the frequency component present in the detected signal.

Accordingly, in a further aspect of the invention, there is provided apparatus for determining non-invasively the presence and/or concentration of blood analytes in an animal comprising:-

a. means for producing a polychromatic light beam;

b. means for modulating the polychromatic light beam such that the modulation frequency is dependent upon the wavelength of light within the beam;

c. means for causing the said modulated light beam to impinge upon a body surface of the animal whereby blood analytes interact with the light beam and perturb the spectral distribution of light within the beam;

d. means for extracting spectral information from the resulting light beam by detecting the beam at a plurality of modulation frequencies, thereby to determine the presence and/or concentration of the said analytes.

The apparatus may preferably be used in accordance with the first aspect of the invention for carrying out measurements on the front part of the eye, but may also be employed on other body surfaces.

The modulating means preferably includes a rotatable grating, means for rotating the grating, and means for producing an image of the grating on the grating, at a position which is displaced in the plane of the grating from the position of the grating by an amount dependent upon the wavelength of the light forming the image. The means for producing an image of the grating on the grating preferably includes a dispersing element, for example a prism.

The use of such an instrument enables the absorption or reflection spectrum of blood analytes to be measured easily at many more wavelengths than is possible with an instrument incorporating discrete interference filters.

It is desirable that spectral measurements should be taken at many wavelengths, particularly when determining the concentration of blood analytes present in small amounts. Standard analytical techniques may be utilized

for deriving concentration data from the spectral measurements made, for example multiple linear regression, partial least squares, or principal components regression.

In accordance with a further aspect of the present invention, it has been determined that infrared signals obtained from an animal in order to determine blood analytes may be enhanced by determining the variation of the said spectrum which is in phase with the pulse of the animal. Similar techniques are conventionally used in so called "pulse oximetry", which are employed to determine blood oxygen content optically. So far as we are aware however, no proposal has ever been made hitherto to enhance the sensitivity of blood analyte determination by infrared spectroscopy by using similar techniques linked to the coronary pulse. Accordingly, in a further aspect of the invention, there is provided apparatus for determining non-invasively the presence and/or concentration of blood analytes in an animal comprising:-

a. means for illuminating a surface of the body of the animal with infrared radiation

b. means for detecting infrared radiation reflected from the said surface and for analyzing the spectrum of the said reflected radiation to determine the presence and/or concentration of the said analytes,

characterised in that the apparatus also includes means for detecting the pulse of the animal, and for analyzing the said spectrum to determine a component of the said spectrum which varies with the said pulse thereby to enhance the determination of blood analytes.

A further aspect of the invention provides a method of determining non-invasively the presence and/or concentration of blood analytes in an animal comprising:-

a. illuminating a surface of the body of the animal with infrared radiation

b. detecting infrared radiation reflected from the said surface and analyzing the spectrum of the said reflected radiation to determine the presence and/or concentration of the said analytes,

characterised in that the method includes the step of detecting the pulse of the animal, and determining the variation of the said spectrum which is in phase with the said pulse.

This aspect of the invention is of most benefit when the NIR spectrum determination is carried out on a part of the body to which the blood supply is highly pulsatile, for example a finger or an ear lobe. The blood supply to the front surface of the eye is relatively non-pulsatile, and therefore this method is of limited value when applied to the front surface of the eye. It is however a benefit to employ this aspect of the invention with the aspect of the invention discussed earlier, relating to the modulation of the light employed, in accordance with its wavelengths.

The techniques of pulse oximetry are well known, and need not be discussed in detail.

A number of preferred embodiments of the various aspects of the invention, all of which may be used separately or together, are illustrated in the accompanying drawings, in which:-

Figure 1 is a schematic diagram of a device according to the invention for measuring blood glucose levels;

Figure 2 is a schematic plan view of a device according to the invention;

Figure 3 is a section on AA of Figure 2;

Figure 4 is a side view of the device of Figure 2;

Figure 5 is a schematic representation of the instrument in use;

Figure 6 illustrates an arrangement for decreasing specular reflection in a device according to Figures 1 and 2;

Figure 7 is a schematic representation of an alternative embodiment, for minimising specular reflection;

Figure 8 illustrates a further alternative method;

Figure 9 is a schematic diagram of the so called "mock interferometer", for modulating a light beam at a frequency dependent upon its wavelengths;

Figure 10 is a schematic diagram of the incorporation of such a modulation device into a device according to the invention for ocular blood analyte determination; and

Figure 11 is a more detailed schematic representation of a device according to the invention incorporating means for modulating a light beam.

Referring in detail to the drawings, Figure 1 is a schematic diagram, illustrating the major components for carrying out glucose measurements on the front surface of the eye, according to the preferred embodiment of the invention. The apparatus of Figure 1 includes a light source 1 (typically a filament lamp such as a tungsten/halogen lamp), reflector 2, and collimating lens 3, for producing a parallel light beam. The parallel light beam is passed through a light modulator 4, which will be described in more detail hereinafter, which modulates the light beam, at a modulation frequency which is dependent upon the wavelength of the light.

The modulated light beam 7 passes through a beam splitter 8, and focusing lens 9, which focuses the modulated beam on the front surface 10 of the eye, for measuring the concentration of blood analytes. The arrangement is such that the focused beam impinges upon an

edge region of the eye, which is particularly well suffused with surface blood vessels.

Diffusely reflected light from the surface 10 is collected by lens 9, and passes back through beam splitter 8, to be focused by lens 11, on detector 12.

A processing unit 5 is provided, linked to detector 12 and to light modulator 4. Processing unit 5 includes a number of electronic filtering circuits, so that the intensity of light reflections at a plurality of modulation frequencies (and consequently at a plurality of infrared wavelengths) may be detected.

The detector 12 may be preferably a non-imaging concentrator. The processing unit 5 may take the form of a microprocessor, and appropriate software.

Processor unit 5 also includes means for carrying out analysis of the resulting absorption bands detected, using for example multiple linear regression, partial least squares, or principal components regression.

The device may also include a pulse detector 6, which enables the pulse of the individual to be detected. Although this is shown schematically in Figure 1, in practice the use of a pulse detector is of less value when carrying out analyte determinations on the front of the eye, since pulsatile variations in the blood supply are relatively small at this point. Such a pulse detector is of considerable value however when determinations are made on other body parts, such as a finger or earlobe. The pulse detector 6 may be of any form conventionally used for pulse oximetry.

Pulse oximetry is a technique for determining the oxygenation of blood using optical absorption measurements on a body part. Typically the red or infrared absorption of a body part is measured at two wavelengths one of which is chosen because it is absorbed equally by oxyhaemoglobin (oxygenated haemoglobin) and deoxyhaemoglobin (deoxygenated haemoglobin) and another because it is absorbed strongly by one form of haemoglobin but only weakly by the other. As the blood pulses through the body the volume present in the tissue increases and decreases cyclically. A pulse oximeter monitors the absorption of the tissue at the two wavelengths caused by increases and decreases in the volume of the blood present in the tissue. The pulsatile component of the absorption is due primarily to the blood in the tissue rather than the surrounding tissues. The ratio of amplitudes of the two pulsatile signals provides a measure of the oxygenation of the tissue.

Processor 5 includes a phase-sensitive detector, linked with the input from pulse detector 6, such that only the component of the detected signal which varies in phase with the detected pulse is passed to the detection circuitry.

Thus, the processor 5 is capable of separating the static and alternating (pulsatile) components of the optical spectrum. The pulsatile component of the spectrum is strongly correlated to the blood absorption spectrum, and thus provides a good basis on which to carry out the calculation of blood analyte concentration.

It is advantageous to link spectral measurements to the blood pulse as the continuously measured spectrum typically contains a great deal of information about the other tissue components whereas the pulsatile component of the spectrum is much more representative of the blood.

Linking the spectral measurements to the pulse could be accomplished, for example, by recording multiple complete spectra each in a period much shorter than the pulse, say one tenth of a second, and then extracting the pulsatile component of the absorption measurement at each wavelength for further analysis.

Figures 2 to 5 illustrate the external appearance of a practical embodiment of a portable device according to the invention. The device of Figures 2 to 4 comprises a body 20, housing the optical components and detection circuitry. The components within body 20 are configured such that the focused beam intended to impinge on the front surface of the eye passes through an aperture 21 in the body 20. Around aperture 21 is a screw-threaded adaptor 22, to which is affixed by means of the screwthread a moulding 23, which is shaped to the facial contours of the user, and includes a flexible eye and nose piece. The shape of the molding 23 ensures that the device is located correctly with regard to the particular facial features of the individual, and that the light beam impinges on the desired location on the front of the eye. A sculpted hand grip 24 is provided for the convenience of the user. The upper surface of the body 20 carries a start button 25, operated by the user, and an LCD screen 26 for displaying the measurements obtained. The general method of use of the device is illustrated in Figure 5.

Although the general layout illustrated in Figures 2 to 5 is particularly suited for use with a detection system as shown in Figure 1, any other detection system capable of obtaining an infrared spectrum from the front surface of the eye may be employed, for example a Fourier Transform spectrometer.

Because specularly reflected light contains far less spectral information about the blood than light which is diffusely reflected (backscattered), it is desirable to incorporate some mechanism for minimising the effects of specular reflection. A simple arrangement is illustrated in Figure 6. In this embodiment, the spatial arrangement is simply arranged so that the focused light beam impinges upon the eye surface at a point 10 where the curvature is such that specular reflection tends to be away from the detection system. The light modulator and processor unit have been omitted, for clarity.

In an alternative embodiment, illustrated in Figure 7, detector 12 is a CCD imaging device, having an array of detection points. In this embodiment, the arrangement includes a beam stop 13 for limiting the width of the collimating beam to enable the detector to gather light from a larger range of angles than is occupied by the specular reflection. The modulator and processing unit are not shown, for clarity. The processing means 5 is programmed and arranged so as to locate the region on the detector 12 at which the specular reflection is received. Normally, the specular reflection will be relatively sharp and produce an intense signal, and it is therefore a straightforward matter to determine the point at which the specular reflection occurs, and to give a lower weighting (or a zero weighting) to the signal received from that region of the detector.

Figure 8 shows an alternative means of suppressing the effects of specular reflection, on the basis of the light polarisation. Only the components of the system relevant to this aspect are shown in Figure 8, for clarity.

Between the lens 3 and lens 9 a polariser 33 is inserted, to polarise the light incident on the eye. The polariser may be a linear polariser, orientated for example

to polarise the light perpendicular to the plane of incidence, or a circular polariser. In the detected beam, an analyzer 30 is positioned between lens 31 and lens 32, so as to block specularly reflected light from the eye. A waveplate may also be used in conjunction with the polarising elements.

Figure 9 is a schematic representation of the so called "mock interferometer" referred to in the reference by Lawrence Mertz, mentioned above, and illustrates the way in which a simple mechanical arrangement can be utilized to modulate a light beam at a frequency which depends upon its wavelengths. A schematic representation of a simple mechanism incorporating such a device in an analyzer in accordance with the invention is illustrated in Figure 10. In the representation of Figure 9, an optical grating 40 having a spacing of approximately ten lines per millimetre is located in a rotating mount, and light is passed through the grating, and focused by a lens 42. A mirror backed dispersing prism 44 reflects the light beam through the lens 42, and forms an image of the grating on the grating surface. Because the position of the image on the grating is dependent upon the wavelengths of the light, the coincidence of the grating lines and image lines, and therefore the chopping or modulation frequency, it is also dependent upon the wavelengths.

Figure 10 shows schematically how such a device may be incorporated into a device according to the invention, the same reference numbers being used as in Figure 1. A more detailed schematic representation of such a device is illustrated in Figure 11. Again, the same reference numbers being used as in Figure 1.

The device includes a polychromatic light source 1 (a tungsten halogen filament lamp), and a reflector 2 and collimating lens 3 as in Figure 1. The collimated light

beam then passes through a light modulator, comprising a disc 40, on the surface of which is an optical grating. The grating may be either a phase grating or an amplitude grating, and has a spacing which is large compared to the wavelength of light (typically a spacing of the order of ten line pairs per millimetre). Disc 40 is rotated at a constant speed by means of an electric motor 41.

An optical system comprising lenses 42, mirrors 43, and a dispersing element 44, is arranged so as to form an image of the rotating grating on the surface of the grating itself. As indicated in Figure 11, the lenses 42 are separated from each other by the sum of their focal lengths f, and are positioned such that the grating is in the focal planes of the lenses closest to it. Because of the presence of the dispersive element 44, the position of the image on the disc 40 depends upon the amount by which the light is dispersed by element 44, and thus upon the wavelength of the light in question. As a result, the light which is transmitted by the grating is chopped or modulated, at a frequency which varies cyclically, but which depends upon the translation of the image in relation to the grating, and thus upon the wavelength of the light.

The modulated light passes through beam splitter 8 and lens 9, is reflected from the front surface of the eye (or any other suitable body part), and detected by detector 12.

Electrical signals from the detector are then analyzed by dividing them into frequency "bins" in a known manner, for example using electronic filters, such as discrete RC circuits tuned to the frequencies of interest, or a lock-amplifier and frequency synthesizer.

Alternatively, the reflection spectrum of the eye may be obtained by transforming the time varying signal using a

Fourier transform with a non-uniform sampling interval (see Lawrence Mertz "Transformations in Optics", John Wylie & Sons, Inc., New York, 1965). A particularly advantageous feature of this type of arrangement is the high optical throughput of the device, as there is no need for the light to pass through a slit. High throughput is a significant advantage for a battery powered instrument, as it minimises the electrical power consumption of the device. It also minimises the time required to make a measurement of analyte concentration to a particular accuracy.

Although the modulation method discussed above is particularly advantageous when utilized in a device for scanning the front surface of the eye, it also has advantages for analyte determination using other parts of the body, for example the retina, choroid, optic nerve head (optic disc), finger, earlobe, lip, or other tissue with a good blood supply. The optic nerve head can be advantageous in some circumstances, because of its good blood supply and pulse, good optical access to blood perfused tissue, very stable temperature, lack of pigmentation, and the ability to use simple optical arrangements taking advantage of the optics of the eye. However, the levels of glucose in the aqueous humor and difficulty in obtaining sufficient light levels restrict the usefulness of the back of the eye in this context. In addition, some forms of eye disease, such as cataracts, make utilization of the retina, choroid or optic nerve head difficult.

As noted above, the wavelength and strength of water absorptions in the near infrared portion of the spectrum vary with temperature. The phenomenon adds to the difficulty of developing a reliable calibration algorithm for the determination of blood analyte concentrations. For some calibration algorithms it is advantageous to measure

the body temperature while developing the algorithm and to use temperature as a variable in the algorithm. Temperature can be measured simply by monitoring the position of the water absorption peak (as described in "Possible Medical Applications of NIR", K.H. Norris, Making Light Work: Advanced in NIR Spectroscopy (4th International Conference on NIR Spectroscopy, Aberdeen 1991), edited Ian Murray and Ian Lowe, VCH, 1992). Accordingly, in a preferred embodiment of the invention, the temperature of the body part under investigation is measured, by measurement of the NIR absorption of water in the region in question. Alternatively temperature can be measured using a thermistor, thermocouple, or other conventional means.

According to a further aspect of the invention, it is desirable to raise or lower the temperature of the body part to a constant temperature to minimise the variability in its spectral properties. Power to the heating or cooling mechanism, which might be an electrical resistor or thermoelectric element respectively, is linked to a temperature sensor, such as those described above, by means of a feedback loop. It is preferable to raise the body temperature rather than to cool it because the body temperature rarely increases by much, whereas it may cool considerably, and because increasing the temperature of the body part increases the amount of blood in the tissue and increases the strength of the pulsatile component of the flow, as shown in "Noninvasive Pulse Oximetry Utilising Skin Reflectance Photoplethysmography", Y. Mendelson and B.D. Ochs, IEEE Transactions on Biomedical Engineering, Vol. 35, No. 10, pp.798-805, October 1988. In a particularly preferred embodiment of the invention, heating of the body part may be achieved by utilising the infrared radiation employed for the spectral determination to heat the body part under investigation.

The simplicity of the device means that measurements can be made of a large number of wavelengths, using suitable calibration algorithms. Different wavelengths can be used for different population groups, or even for different individuals, further enhancing the ability of the instrument to measure accurately the blood glucose or other blood analyte concentration.

Because the preferred embodiment of the invention disclosed above does not use discrete interference filters, and can be tuned to examine any wavelength, the instrument itself can be used for the purposes of calibration.

The derivation of appropriate calibration algorithms for various blood analytes is simply a matter of deriving a suitably large data set for known patients of varying blood analyte concentration, and obtaining appropriate correlations between absorption at various frequencies, and the blood analyte concentrations, using any of the techniques noted above. The methods disclosed may also be employed in the determination of other blood analytes, for example alcohols and in particular ethanol, urea, total and high density cholesterol, haemoglobin, oxyhaemoglobin, low and high density lipoproteins, triglycerides, total protein, albumin, and globulins in serum.

Claims

1. Apparatus for determining non-invasively the presence and/or concentration of blood analytes in an animal comprising:-

a. means for illuminating a surface of the body of the animal with infrared radiation

b. means for detecting infrared radiation reflected from the said surface and for analysing the spectrum of the said reflected radiation to determine the presence and/or concentration of the said analytes,

characterised in that the said surface is the front surface of the eye, and in that the apparatus includes means for locating the illumination means and/or the detecting means in a fixed location with respect to facial features of the animal.

2. Apparatus as claimed in Claim 1, wherein the location means comprises a moulding shaped to fit the particular face contours of the animal.

3. Apparatus as claimed in Claim 2, wherein the location means comprises a moulding shaped to fit the eye socket and/or nose of the animal.

4. Apparatus as claimed in Claim 2 or Claim 3, wherein the location means comprises a mounting assembly for the illumination means and detecting means, and means for fixing the said mounting assembly to the said molding shaped to the facial contours of the animal.

5. Apparatus as claimed in any one of the preceding claims, wherein either or both of the illumination means and detecting means are adapted to focus on the edge

regions of the eye which are particularly strongly supplied with blood vessels.

6. Apparatus as claimed in any one of the preceding claims, wherein the illumination means and the detector are positioned on the device such that specular reflection is substantially eliminated.

7. Apparatus as claimed in any one of the preceding claims, wherein the detector is capable of detecting spatial variations in the reflected signal, and of compensating for the effect of specular reflection.

8. Apparatus as claimed in any one of the preceding claims, wherein the illumination means and/or the detector includes means for discriminating between diffuse reflection and specular reflection from the eye surface based on the difference in polarization of the diffusely and specularly reflected light.

9. Apparatus for determining non-invasively the presence and/or concentration of blood analytes in an animal comprising:-

a. means for producing a polychromatic light beam;

b. means for modulating the polychromatic light beam such that the modulation frequency is dependent upon the wavelength of light within the beam;

c. means for causing the said modulated light beam to impinge upon a body surface of the animal whereby blood analytes interact with the light beam and perturb the spectral distribution of light within the beam;

d. means for extracting spectral information from the resulting light beam by detecting the beam at a plurality of modulation frequencies, thereby to determine the presence and/or concentration of the said analytes.

10. Apparatus as claimed in Claim 9, wherein the modulating means includes a rotatable grating, means for rotating the grating, and means for producing an image of the grating on the grating, at a position which is displaced in the plane of the grating from the position of the grating, by an amount dependent upon the wavelength of the light forming the image.

11. Apparatus for determining non-invasively the presence and/or concentration of blood analytes in an animal comprising:-

a. means for illuminating a surface of the body of the animal with infrared radiation

b. means for detecting infrared radiation reflected from the said surface and for analysing the spectrum of the said reflected radiation to determine the presence and/or concentration of the said analytes,

characterised in that the apparatus also includes means for detecting the pulse of the animal, and for determining the variation of the said spectrum which is in phase with the said pulse, thereby to improve the detection of analytes present in the blood.

12. Apparatus for determining non-invasively the presence and/or concentration of blood analytes in an animal comprising:-

a. means for illuminating a surface of the body of the animal with infrared radiation

b. means for detecting infrared radiation reflected from the said surface and for analysing the spectrum of the said reflected radiation to determine the presence and/or concentration of the said analytes,

characterised in that the apparatus also includes means for detecting the pulse of the animal, and for analysing the said spectrum to determine a component of the said spectrum which varies with the said pulse thereby to enhance the determination of blood analytes.

13. A method for determining non-invasively the presence and/or concentration of blood analytes in an animal which method comprises,

a. illuminating a surface of the body of the animal with infra red radiation, and

b. detecting infrared radiation reflected from the said surface and analysing the spectrum of the said reflected radiation to determine the concentration of the said analytes,

characterised in that the said surface is the front surface of the eye.

14. A method of determining non-invasively the presence and/or concentration of blood analytes in an animal comprising:-

a. illuminating a surface of the body of the animal with infrared radiation

b. detecting infrared radiation reflected from the said surface and analysing the spectrum of the said reflected radiation to determine the presence and/or concentration of the said analytes,

characterised in that the method includes the step of detecting the pulse of the animal, and determining the variation of the said spectrum which is in phase with the said pulse.

15. A method of determining non-invasively the presence and/or concentration of blood analytes in an animal comprising:-

a. modulating a polychromatic light beam such that the modulation frequency is dependent upon the wavelength of light within the beam;

b. causing the said modulated light beam to impinge upon a body surface of the animal whereby blood analytes interact with the light beam and perturb the spectral distribution of light within the beam;

c. extracting spectral information from the resulting light beam by detecting the beam at a plurality of modulation frequencies, thereby to determine the presence and/or concentration of the said analytes.

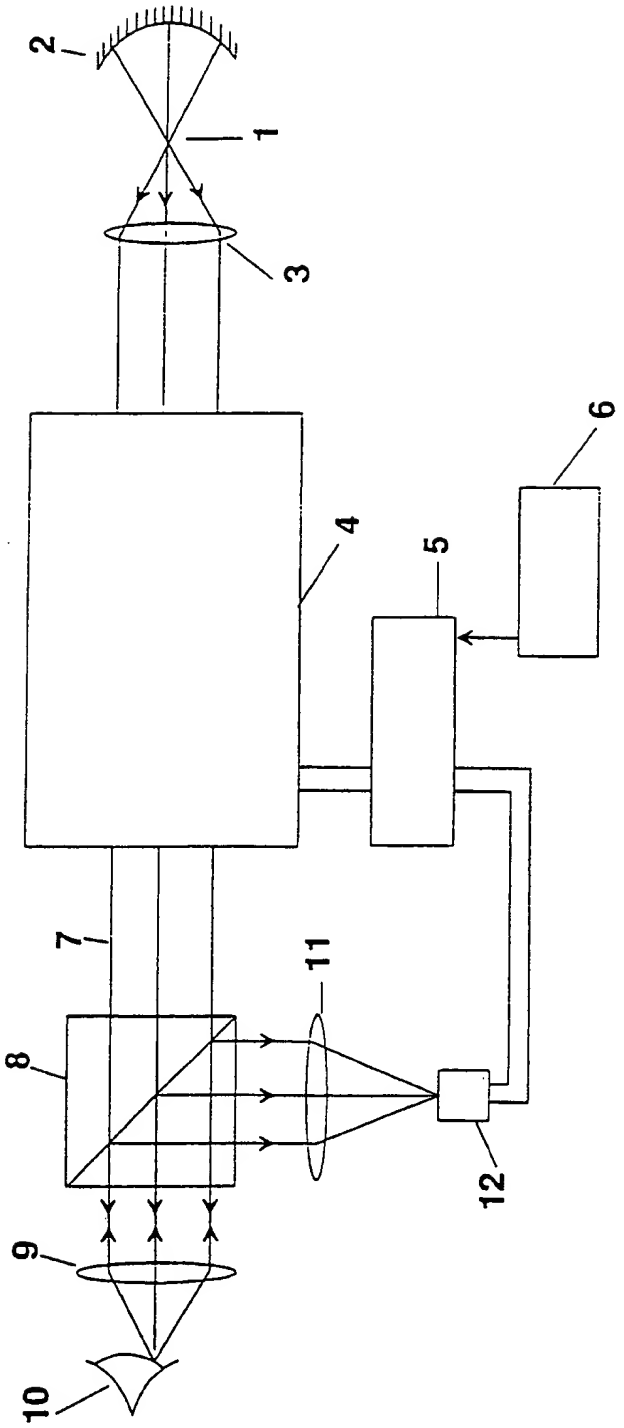


Figure 1

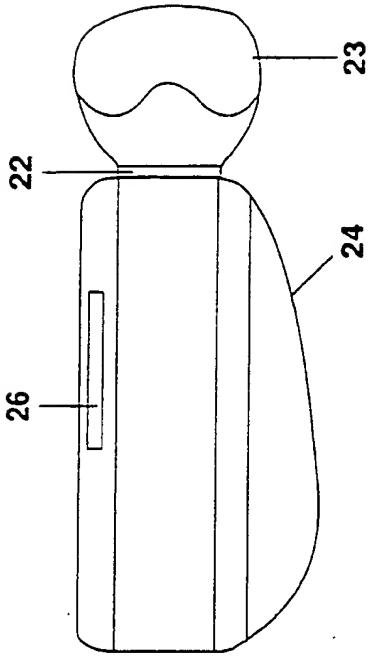


Fig 4

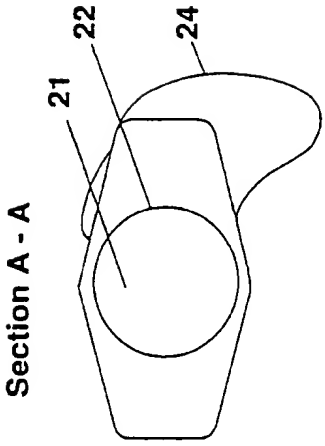


Fig 3

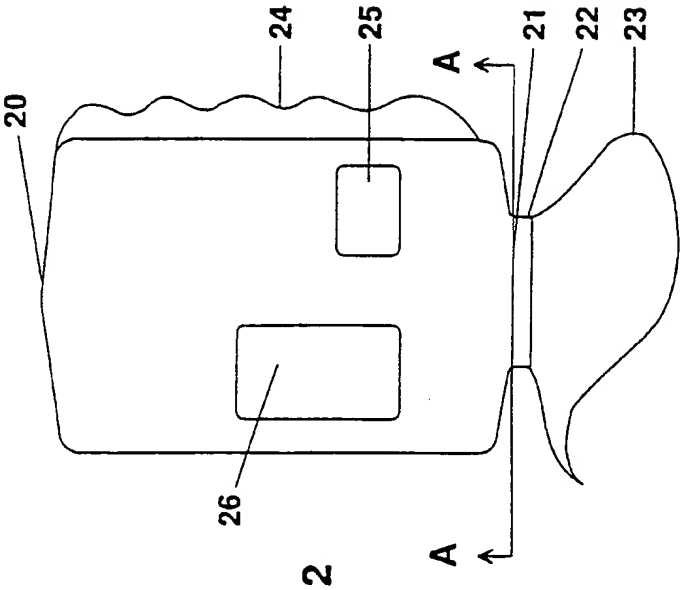


Fig 2

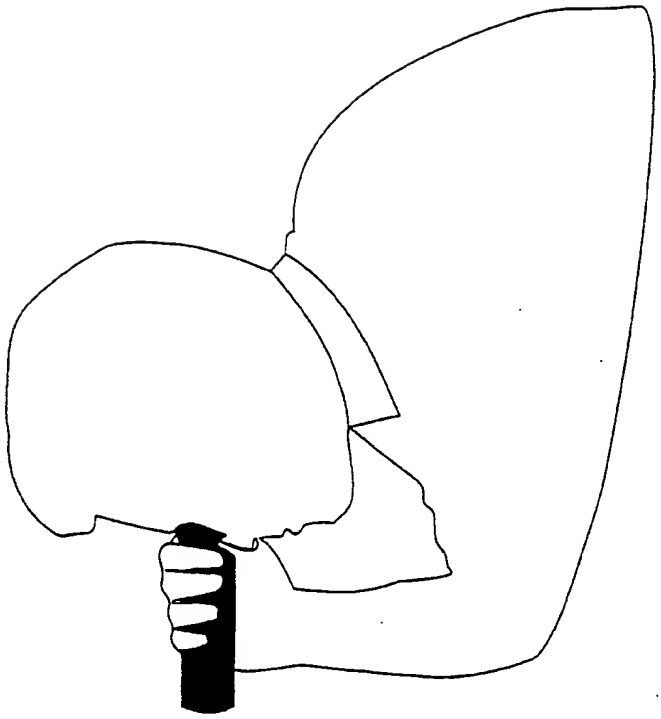

Fig 5

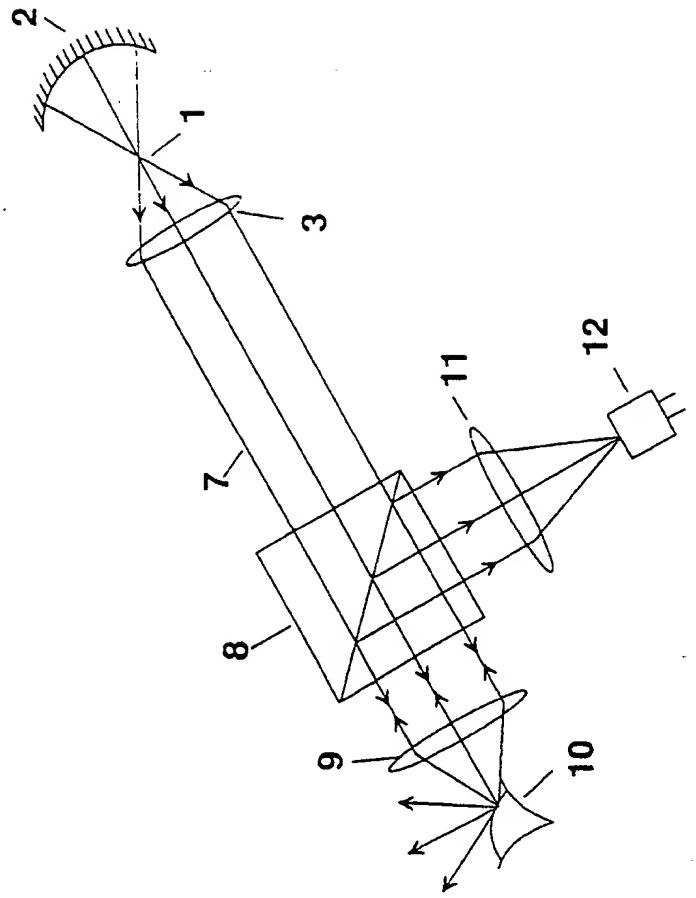


Figure 6

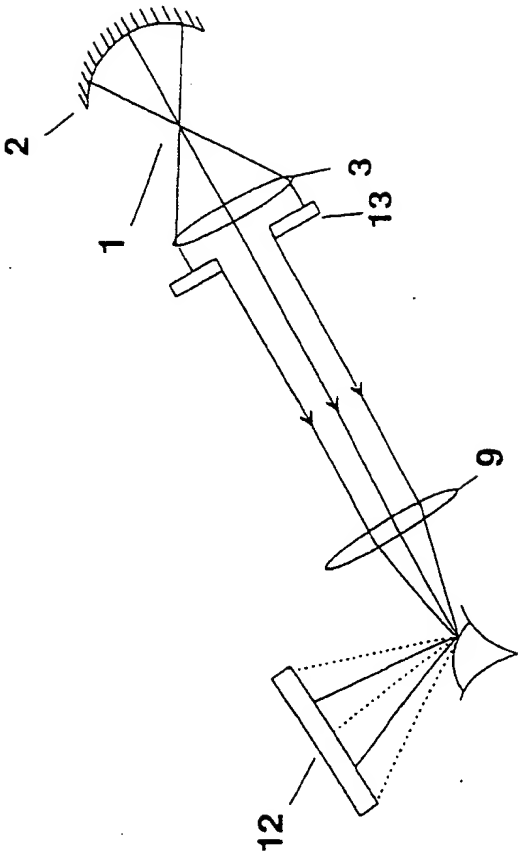


Figure 7

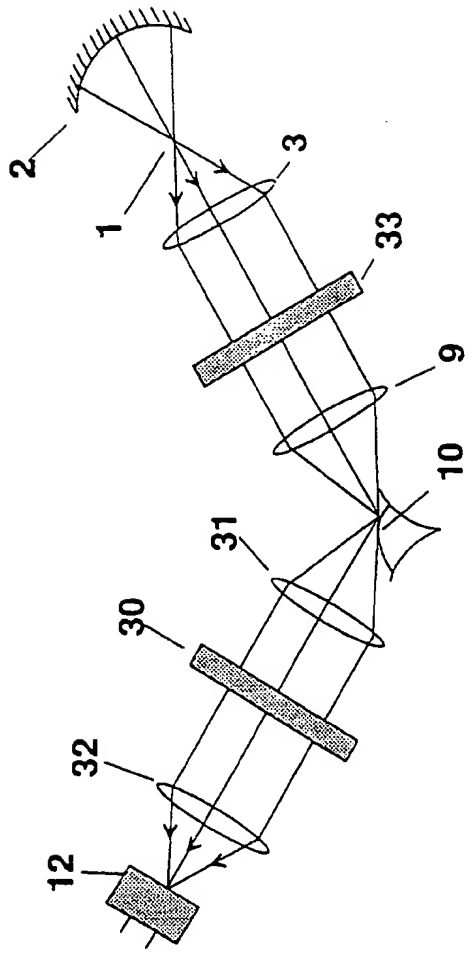


Figure 8

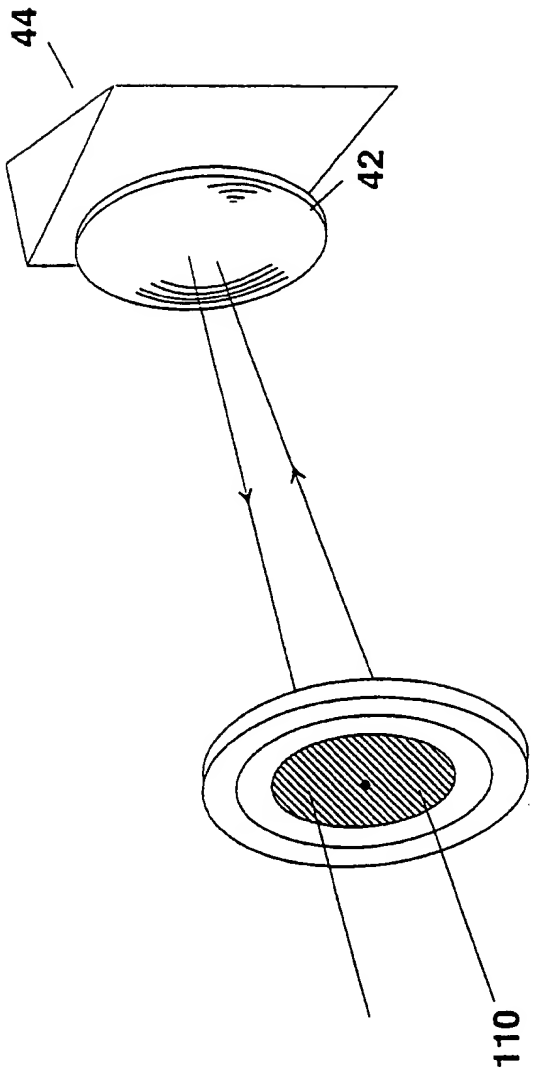


Figure 9

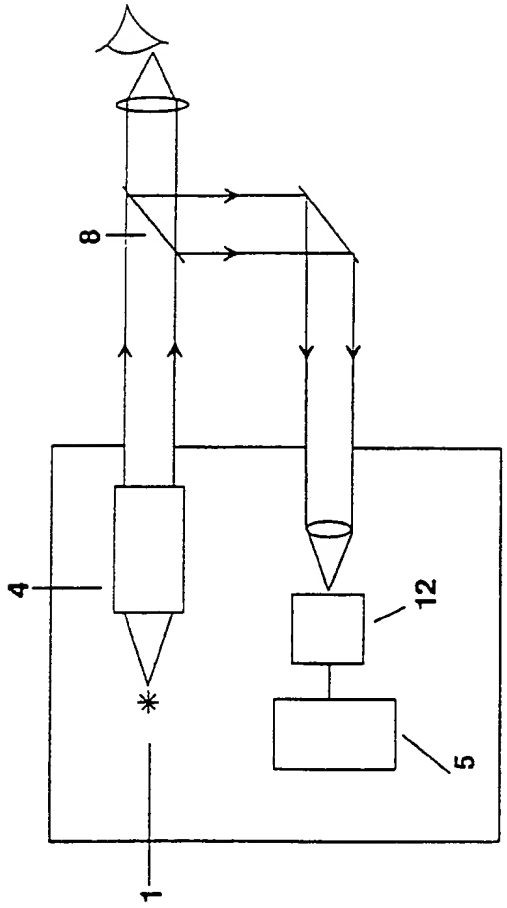


Figure 10

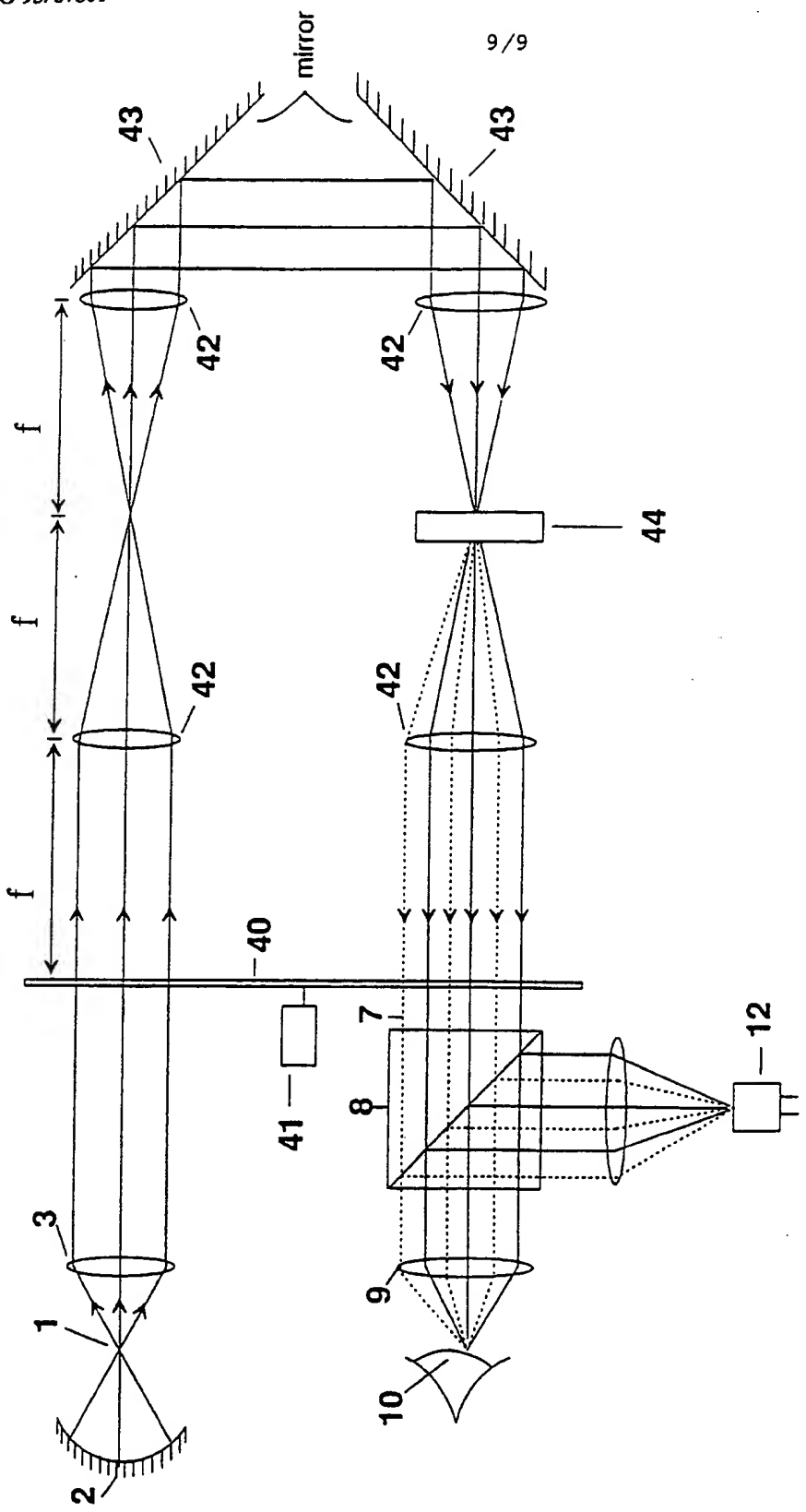


Figure 11

# INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 92/01894

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 B 5/00

## II. FIELDS SEARCHED

Minimum Documentation Searched[7]

| Classification System | Classification Symbols |
|---|---|
| IPC5 | A 61 B |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category * | Citation of Document,[11] with indication, where appropriate, of the relevant passages[12] | Relevant to Claim No.[13] |
|---|---|---|
| X | US, A, 4350163 (NORMAN C. FORD, JR. ET AL) 21 September 1982, see figure 1; claim 5 | 1,13 |
| X | US, A, 4014321 (WAYNE F. MARCH) 29 March 1977, see column 2, line 42 - line 56 | 1,13 |
| A | US, A, 5025785 (JEFFREY N. WEISS) 25 June 1991, see the whole document | 1-15 |
| A | EP, A1, 0426358 (YANG, WON SUCK) 8 May 1991, see the whole document | 1-15 |

* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 13th January 1993 | 26. 01. 93 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| EUROPEAN PATENT OFFICE | ANDERS HOLMBERG |

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

| Category * | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No |
|---|---|---|
| A | US, A, 5054487 (RICHARD H. CLARKE) 8 October 1991, see the whole document | 1-15 |

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/GB 92/01894

SA 65489

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 02/12/92
The European Patent office is in no way liable for theseparticulars which are merely given for the purpose of information.

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| US-A- 4350163 | 21/09/82 | NONE | |
| US-A- 4014321 | 29/03/77 | DE-A- 2538985 | 26/05/76 |
| | | GB-A- 1521113 | 09/08/78 |
| | | JP-A- 51075498 | 30/06/76 |
| | | US-A- 3958560 | 25/05/76 |
| US-A- 5025785 | 25/06/91 | JP-A- 59131326 | 28/07/84 |
| | | US-A- 4883351 | 28/11/89 |
| | | US-A- 4895159 | 23/01/90 |
| EP-A1- 0426358 | 08/05/91 | CA-A- 2028261 | 29/04/91 |
| | | CN-A- 1051297 | 15/05/91 |
| | | JP-A- 3146032 | 21/06/91 |
| US-A- 5054487 | 08/10/91 | AU-D- 7302991 | 21/08/91 |
| | | WO-A- 91/11136 | 08/08/91 |